
Syndrome of the month

Edited by D Donnai and R Winter

Tetrasomy 12p (Pallister-Killian syndrome)

Albert Schinzel

First described in 1977 by Pallister *et al*¹ and independently reported in 1981 by Killian and Teschler-Nicola,² the syndrome is known for its many anomalies and by various names including Pallister mosaic syndrome, Pallister-Killian syndrome, Pallister-Killian-Teschler-Nicola syndrome, Killian-Teschler-Nicola syndrome, and others. Some early cases were misinterpreted as mosaic tetrasomy 21q.³⁻⁵ It is one of the chromosome aberrations in which clinical recognition is important in order to initiate the necessary cytogenetic investigations from different tissues.

Clinical features

These are highly distinctive, especially the combination of a very coarse face, pigmentary skin anomalies, localised alopecia, profound mental retardation, and seizures, and the relatively frequent occurrence of diaphragmatic defects and supernumerary nipples.

CRANIOFACIAL DYSMORPHIC FEATURES (FIGS 1 AND 2)

Although the facies is characteristic from birth onwards, its coarseness becomes more pronounced with age. Frequent features include frontal bossing with a high frontal hairline, temporofrontal balding and sparseness or even absence of lateral or medial eyebrows and eyelashes, and low set and dysplastic ears. Hypertelorism is noted with a wide and flat nasal bridge, exophthalmos and shallow upper orbital ridges, upward slanting palpebral fissures, and inner epicanthic folds. The nose is small with upturned nares, the cheeks are full, and the philtrum is long and simple with a prominent upper lip. There is a large mouth with downturned corners and a high

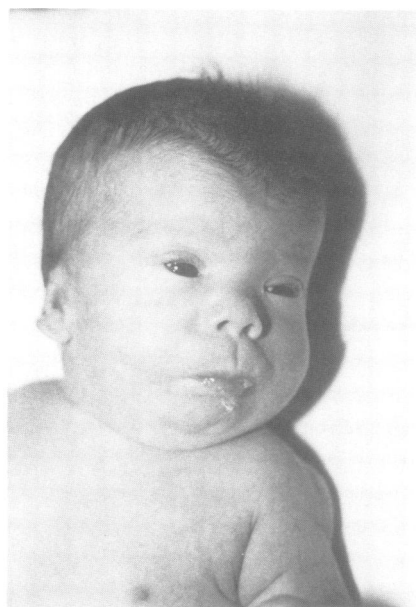


Figure 1 3 week old girl (courtesy of Dr Dian Donnai, Manchester).

arched palate with prominent lateral ridges. The mandible is initially short, but in adults tends to become large and prominent; the neck is short and often webbed with excess nuchal skin.

LIMBS

Disproportionate shortness of the upper and lower extremities has been reported in quite a number of cases and may have escaped attention in others.

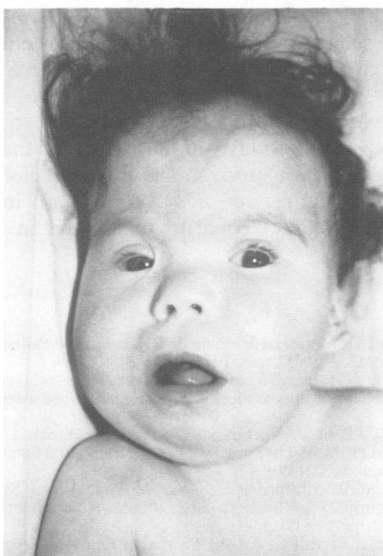


Figure 2 1 year old girl (courtesy of Dr Dian Donnai, Manchester).

Although both mesomelic and rhizomelic shortening are mentioned, the latter seems more frequent. Radioulnar synostosis has been reported once.⁶ The hands and feet are small and broad, with short fingers and toes and tapering fingers. Postaxial polydactyly of fingers,⁷ absence of talus and duplication of halluces,⁸ and postaxial polydactyly of the toes⁹ have occasionally been observed.

Major structural anomalies

FACE AND EYES

Ocular malformations have occasionally been observed including microphthalmia,^{9 10} cataract and keratoconus,¹ pinpoint pupils, and aniridia.¹¹ Cleft lip and palate¹⁰ and cleft palate⁹ were present in single patients. One child had a lower lip pit.¹¹

CARDIORESPIRATORY SYSTEM

Approximately one quarter of reported patients had congenital heart defects. VSD was the most frequent single malformation; others included coarctation of the aorta, PDA, ASD, and aortic stenosis.^{9 11} One patient had hypertrophic cardiomyopathy.⁷ Secondary lung hypoplasia is found in cases with diaphragmatic defects (see below), and a pulmonary segmentation defect was described in one necropsied case.

ABDOMINAL MALFORMATIONS

Congenital diaphragmatic defect leading to diaphragmatic hernia is a highly specific and frequent finding, often causing early postnatal death. The diagnosis may be missed in many newborns with this malformation together with other anomalies who die early and do not undergo fibroblast chromosome examination after a blood lymphocyte chromosome examination has given a normal result. It may, on the other hand, be made prenatally after ultrasonographic detection of the hernia¹² (personal observation), especially since the additional chromosome is likely to be present in amniocytes. The second most frequent gastrointestinal anomaly is anal atresia^{6 11 13} or stenosis⁹ or anteriorly placed anus.^{8 11}

RENAL MALFORMATIONS

Malformations of the kidneys are only occasionally described; cystic kidneys⁴ and dysplastic kidneys¹⁰ have been reported but the incidence of minor anomalies is unknown.

GENITAL MALFORMATIONS

Males may display cryptorchidism and a small scrotum. Female external genitalia are mostly normal; however, ambiguous external genitalia, hypoplasia of

the labia majora, and absence of the upper vagina and uterus have occasionally been reported.¹¹

SKELETAL MALFORMATIONS

Rhizomelic brachymelia is probably quite common. Rarer findings include atlanto-occipital fusion^{4,8} and absence of the twelfth pair of ribs.

SKIN

A characteristic finding in newborns and young children is frontotemporal alopecia and sparseness of the eyebrows and eyelashes. Also characteristic, but mostly observed only from infancy onwards, is patchy, rarely diffuse hyper- or, more often, depigmentation. This finding may be detectable only on Woods light examination. Accordingly, some patients have primarily been classified as having 'hypomelanosis of Ito with additional anomalies'. Accessory nipples are probably quite common.

Motor and mental development: CNS and neurology

There is hypotonia from birth and severe to profound mental and motor retardation from early infancy. The majority of patients will develop a seizure disorder, mostly starting in early infancy. Many are bedridden and almost all will never talk or become continent. There are a few reports of brain necropsy which were mostly normal; cerebellar hypoplasia was mentioned once.⁸ One patient reportedly showed autistic features, but no mention of specific behavioural features was made in other reports.

Growth, survival, and features arising with age

A few patients have been picked up at prenatal chromosome examination because of diaphragmatic defects¹² (personal observation, 1986), hydrops, or hydrocephalus.^{14,15} Complicated pregnancies, prematurity, abnormal presentation at birth, asphyxia, and absence of one umbilical artery are frequent. Measurements at birth are mostly appropriate for gestational age, and only approximately one-third of survivors show diminished growth and fewer show microcephaly. Probably a significant proportion of affected patients die prenatally, perinatally, or early postnatally, and many die even after 10 or 15 years. The oldest patient observed so far, the first of the initial publication, was aged 45 years at last examination.^{1,11}

Some characteristic alterations in the clinical pattern occur during life. Frontotemporal alopecia diminishes or disappears after a few years. The facies gets increasingly coarse, the lips thicken, the tongue

increases in size and protrudes as in Down's syndrome, and the mandible becomes large and protruding. Rarely, kyphoscoliosis and joint contractures develop.

Cytogenetics

Non-mosaic tetrasomy 12p is probably incompatible with intrauterine survival, and this is one of the reasons why the aberration has been discovered both so late and independently of clinical patterns, without recognition of the chromosome aberration in fibroblasts.² All three cases with non-mosaic additional isochromosomes 12p were diagnosed prenatally from amniocytes, and in none of them could lymphocytes later be examined.^{12,14,15} The incidence of metaphases containing the extra chromosome is mostly 0 to 2% in lymphocytes, 50 to 100% in fibroblasts, and 100% in amniocytes and bone marrow cells.⁷ The incidence of 12p tetrasomic metaphases is said to be higher in the fibroblasts cultured from areas of altered pigmentation.¹⁶ The additional chromosome has so far always been a metacentric marker, either an isochromosome or a 12p;12p translocation chromosome.¹⁷ As is to be expected in isochromosomes, the aberration always occurs sporadically. Some earlier cases were initially misinterpreted as mosaic tetrasomy 21, an aberration that probably does not exist.^{3-5,14} Additional confirmation of the origin was provided from gene dosage measurements (normal SOD-1,^{3,8} increased LDH-B⁸) and from analysis of molecular markers on 12p.^{12,17,18} In a number of cases with the phenotype of the Pallister-Killian syndrome, lymphocyte chromosome examinations gave normal results, and no fibroblasts were investigated to confirm the diagnosis^{2,19}; in one, both lymphocyte and fibroblast karyotypes were normal 46,XX.²⁰ The proportion of tetrasomic cells in lymphocytes and fibroblasts apparently does not correlate with the severity of the congenital malformations, the extent of survival, and the degree of mental deficiency. Wenger *et al*²¹ showed an increased maternal age, about equal to that found in Down's syndrome.

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